Long- and short-range connectivity and neuronal types affect prefrontal dorsal raphe circuit dynamics differently

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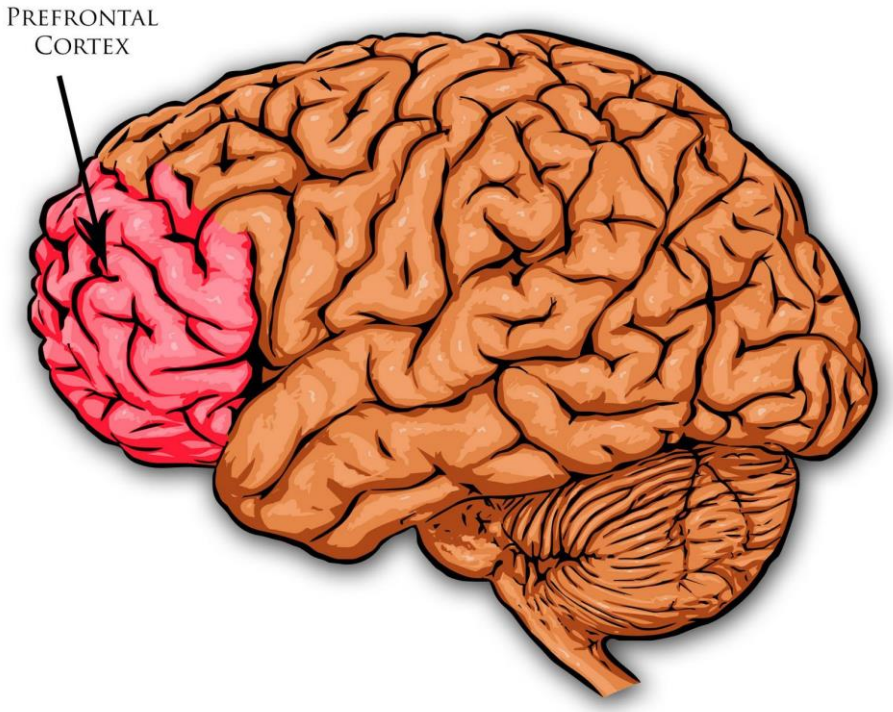
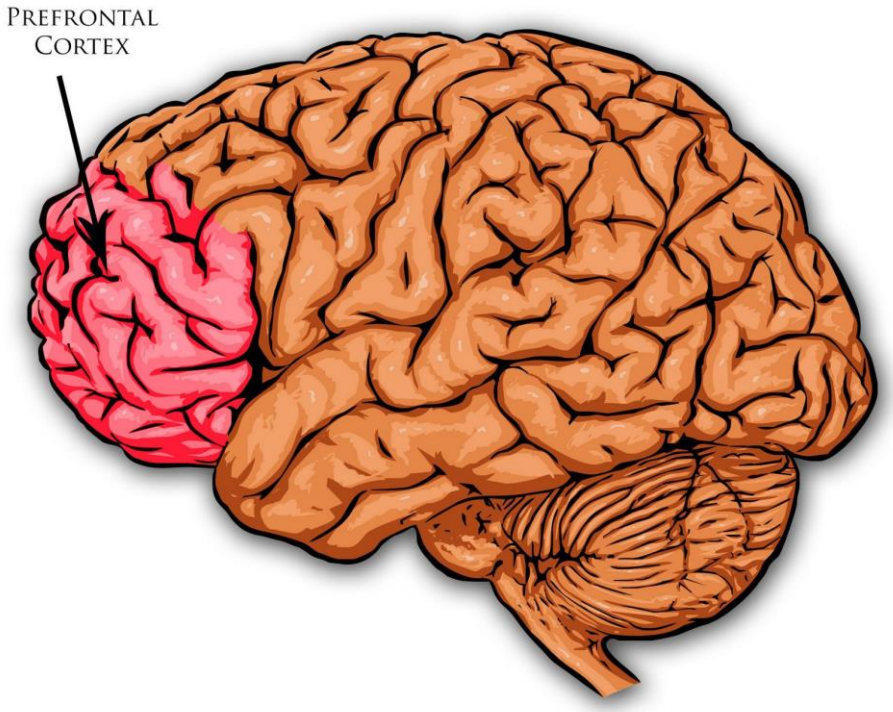
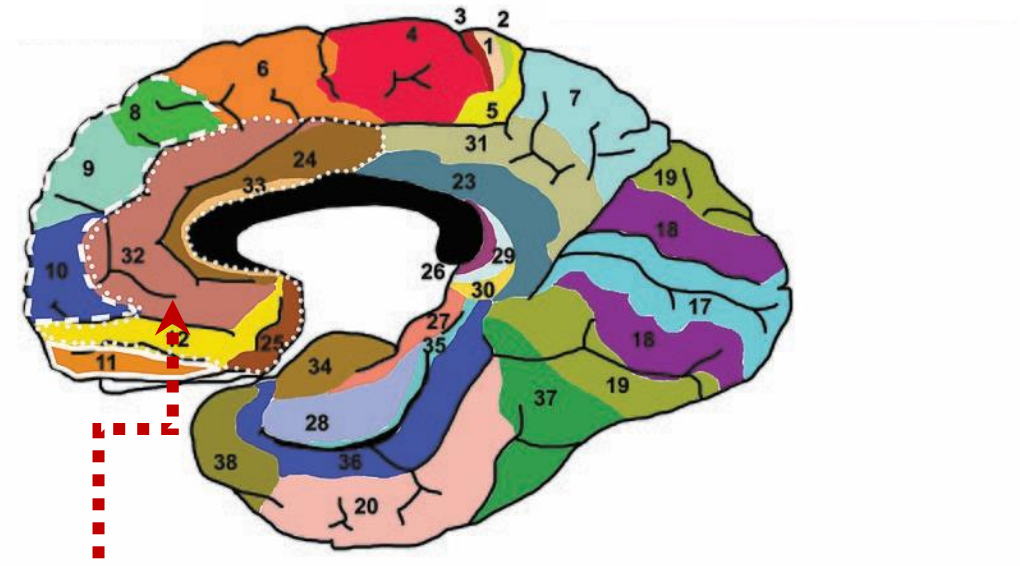
Prefrontal cortex



Prefrontal cortex (PFC) plays a key role in high-level cognitive functions such as attention, memory, decision-making, and mood regulation.

Prefrontal cortex

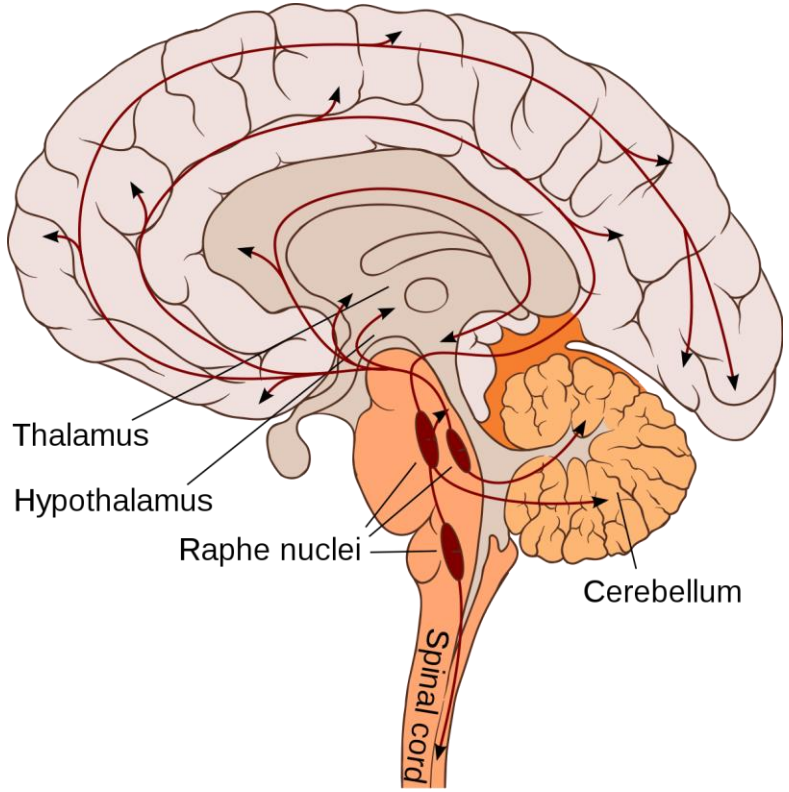




Medial prefrontal cortex (mPFC):
Brodmann areas 12, 24, 25, 32, 33

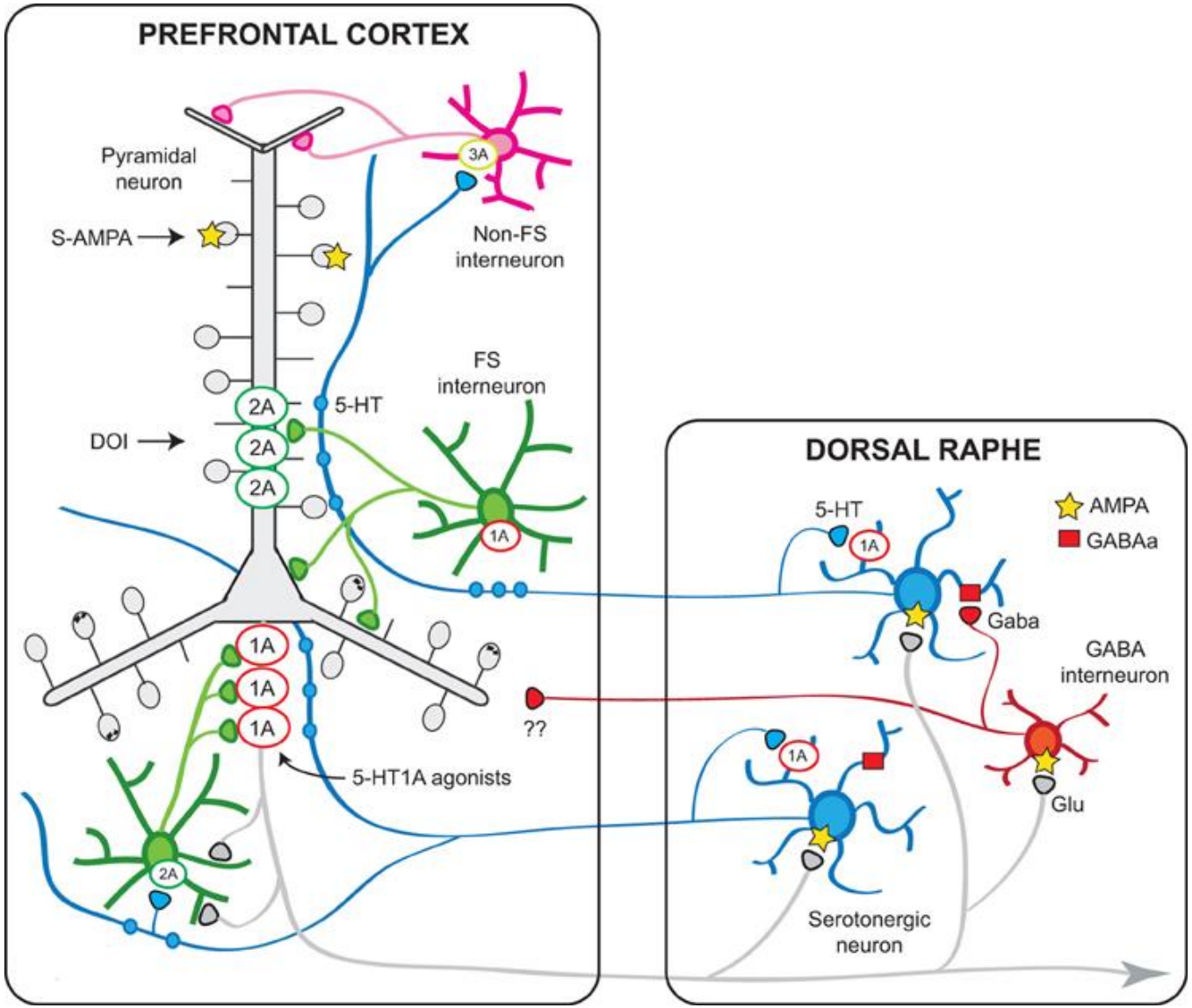
Prefrontal cortex (PFC) plays a key role in high-level cognitive functions such as attention, memory, decision-making, and mood regulation.

Dorsal raphe nucleus (DRN)



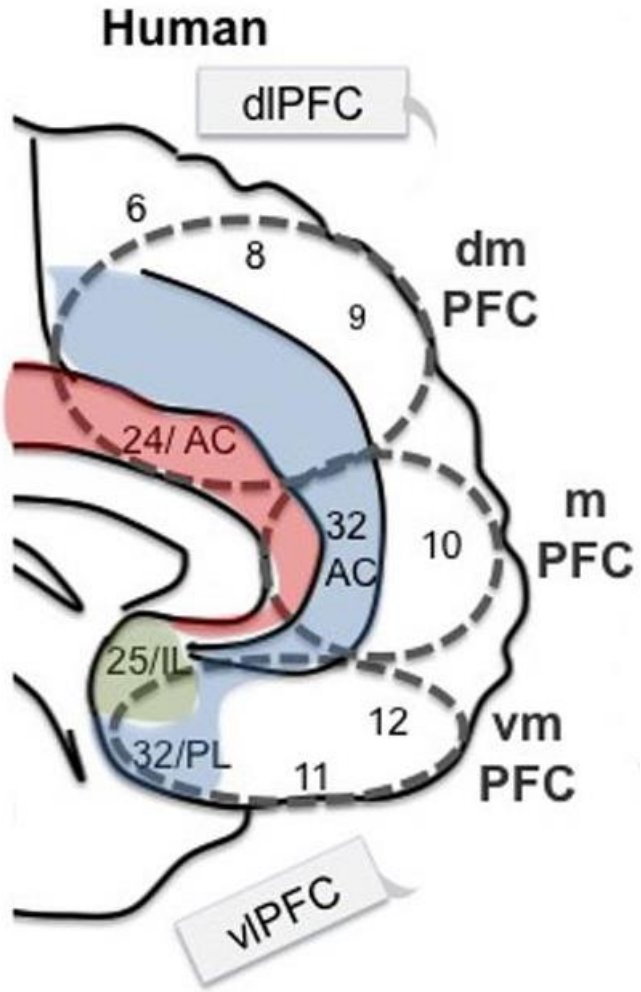
- PFC receives dense serotonergic (5-HT) innervation from DRN.
- DRN is located in the midbrain and pons.

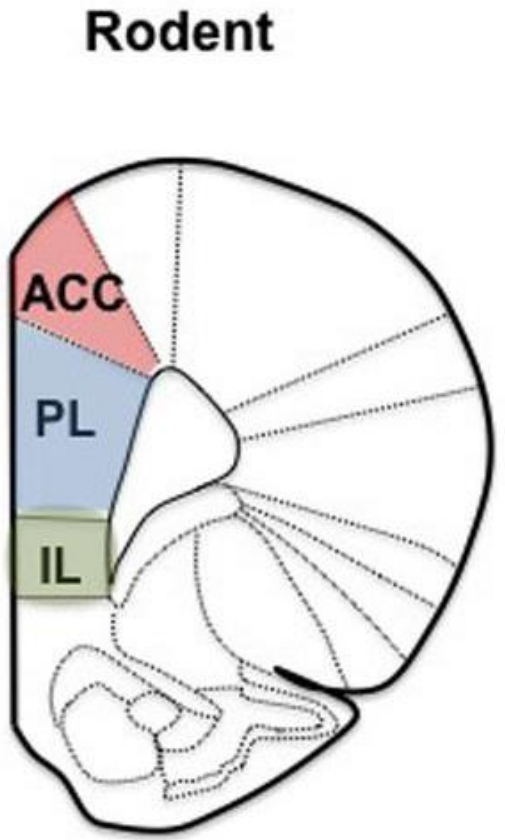
PFC-DRN interaction (closed loop)



(Celada, Puig and Artigas 2013)

Medial prefrontal cortex- Prelimbic cortex (PL)



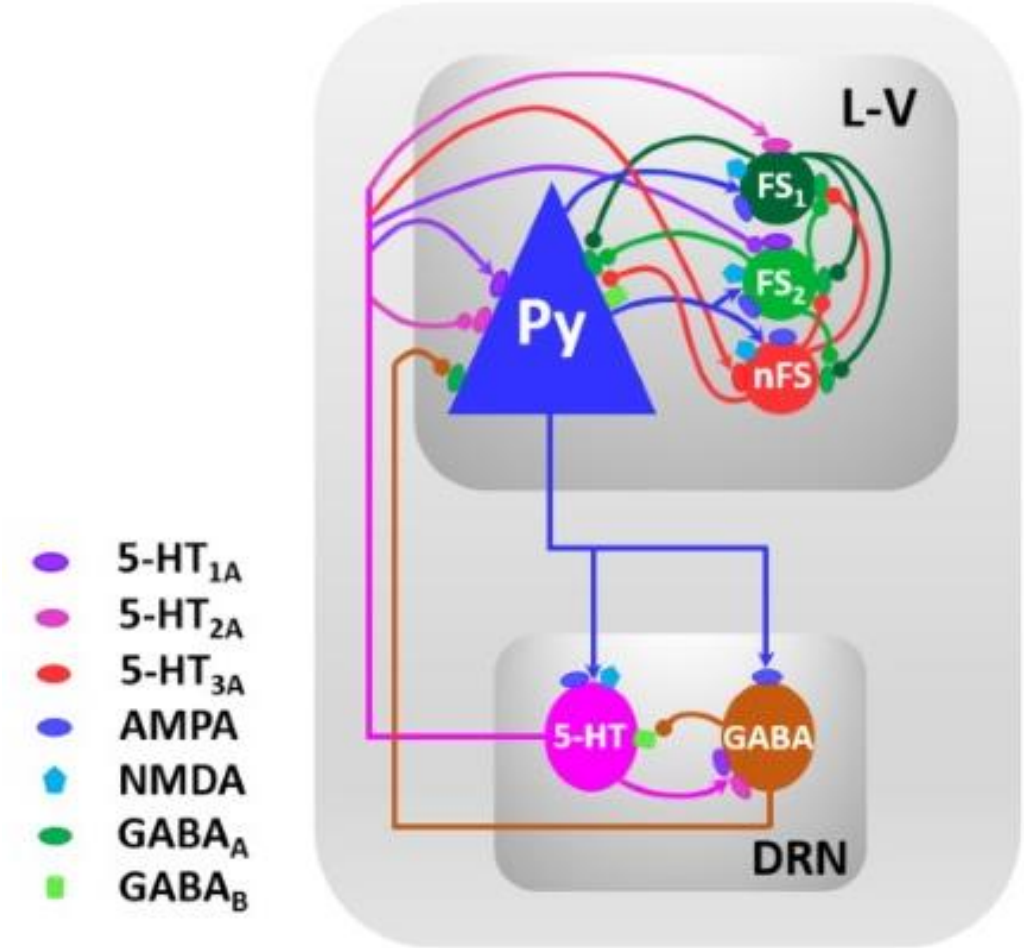


Bicks et al., 2015

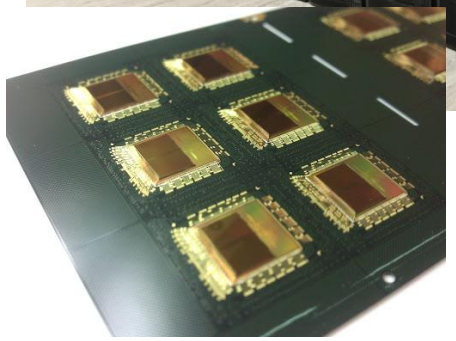
Research Questions

- What is the collective dynamics of PFC-DRN interaction? With the focus on PL-DRN system?
- How the long- and short-range connections in PL-DRN contribute to its collective dynamics?
- What is the role of PL and DRN neuronal types?

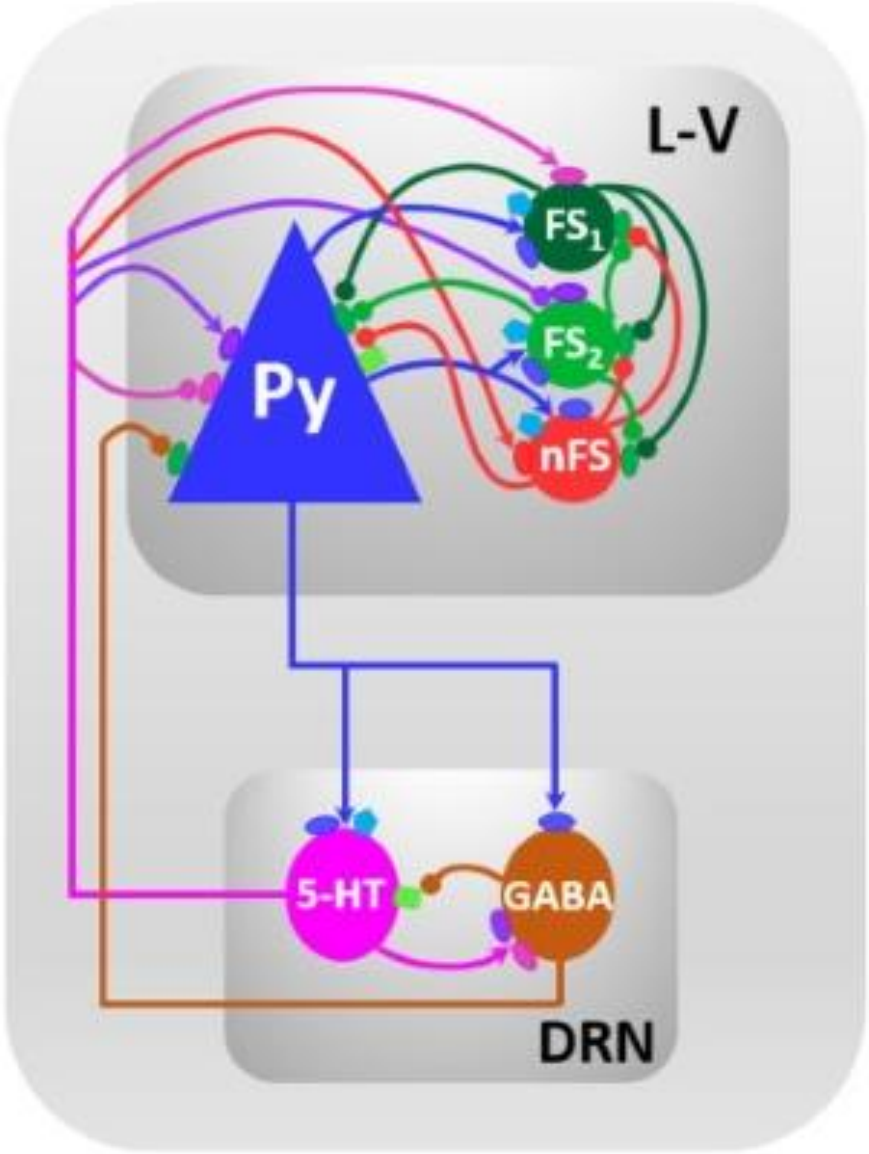
PL-DRN interaction



PL-DRN interaction



SpiNNaker
(University of
Manchester)



L-V

of Py neurons ~ 6300
# of FS1/FS2 neurons ~389
# of nFS neurons ~81

DRN

of 5-HT neurons ~ 13250
# of GABA neurons ~ 6625

Computational model

Single neuron model: Izhikevich type model:

$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 - U + I_{DC,i} + I_{Background,i} + I_{Syn,i}$$

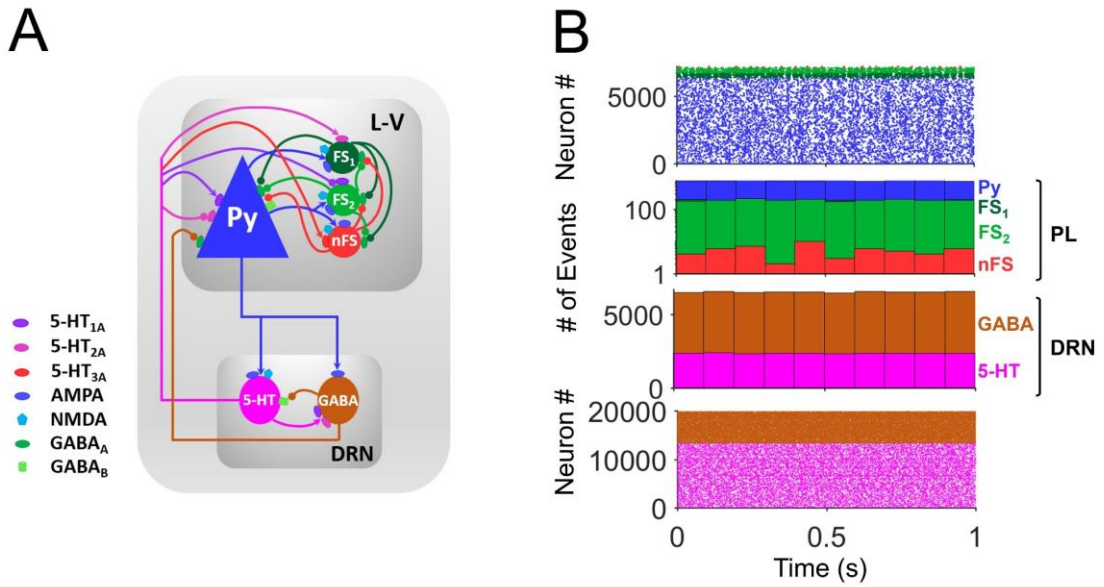
$$\frac{dU}{dt} = \mathrm{a}(\mathrm{b}V - U) \qquad \text{If } V \geq V_{Peak}, \text{then } V = c \text{ and } \mathrm{U} = U + d$$

Synaptic current:

$I_{Syn} = wf\left(e^{-t/\tau_1} - e^{-t/\tau_2}\right)$, *w* is synaptic weight, *f* is scaling factor

τ_1, τ_2 are time constants estimated from experiments for different synapses

Baseline PL-DRN neural activities with multiple network frequency bands can co-exist.



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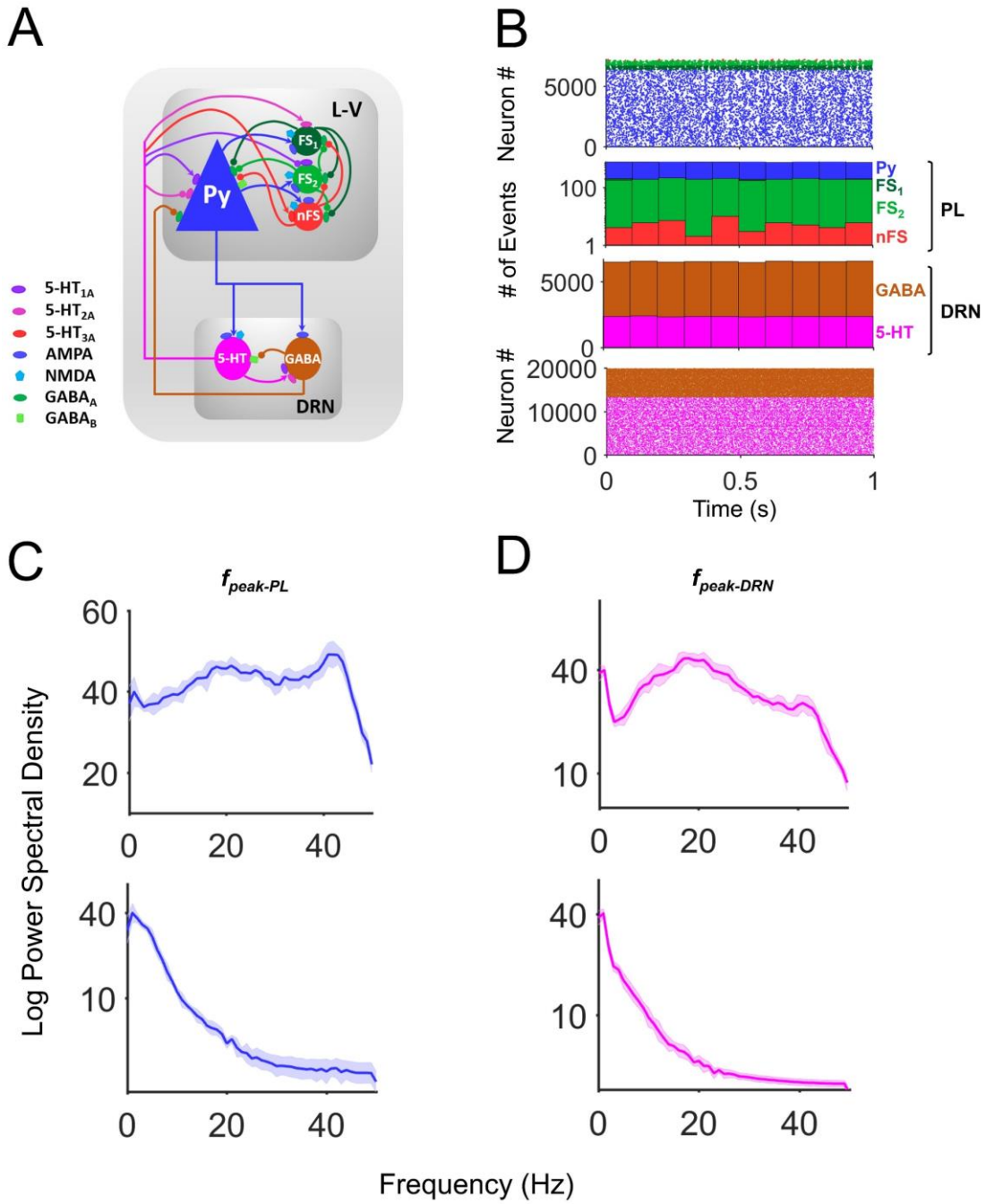
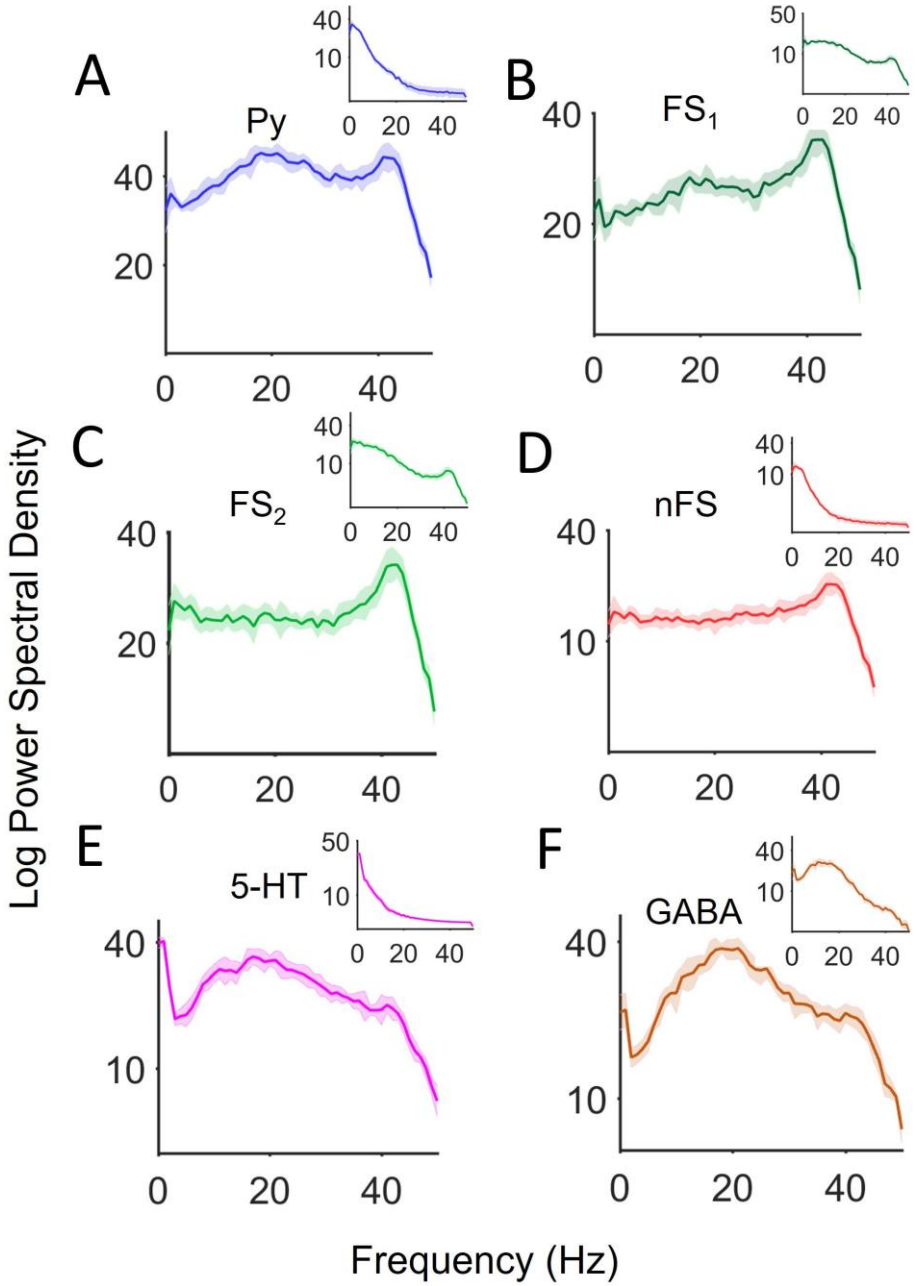
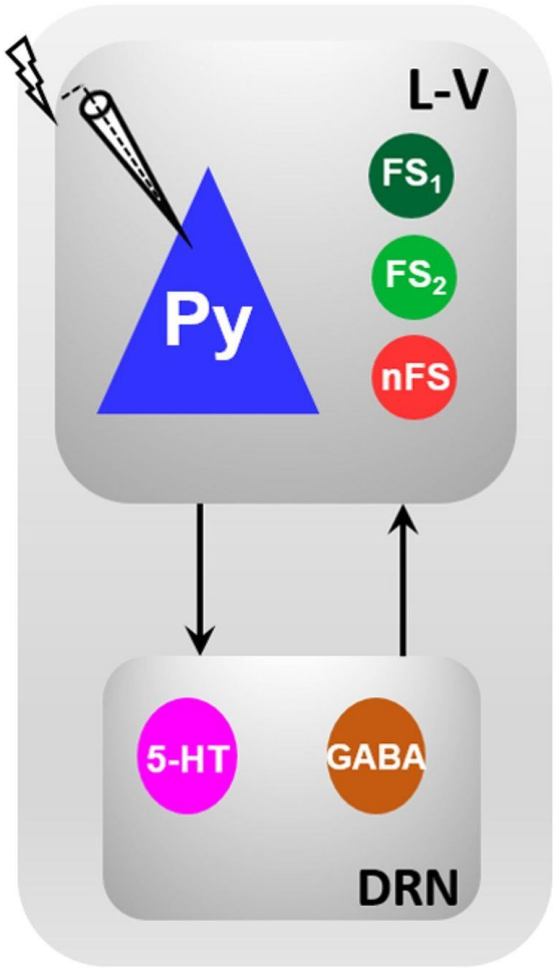
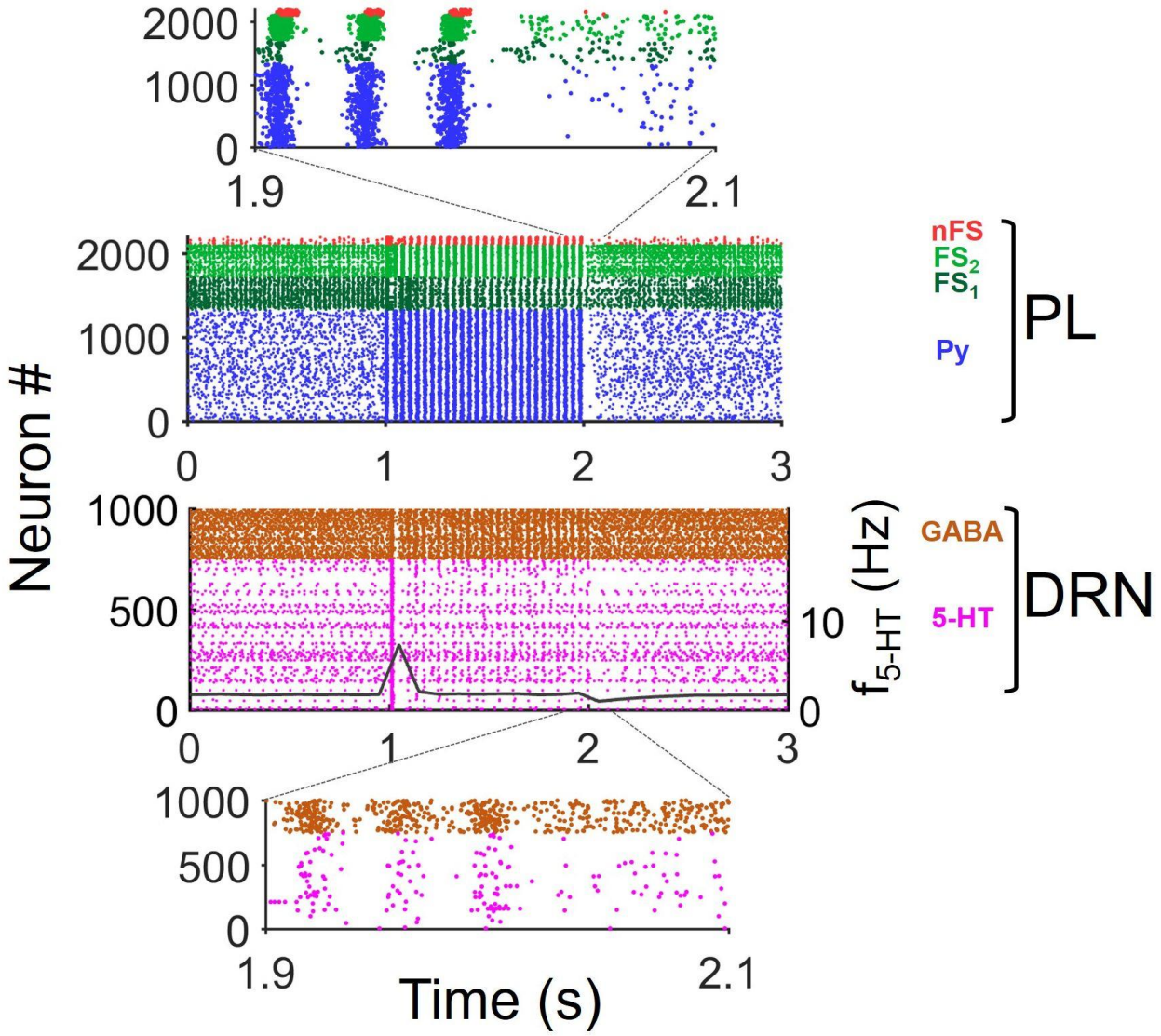


Multiple network frequency bands co-exist for distinct neuronal populations

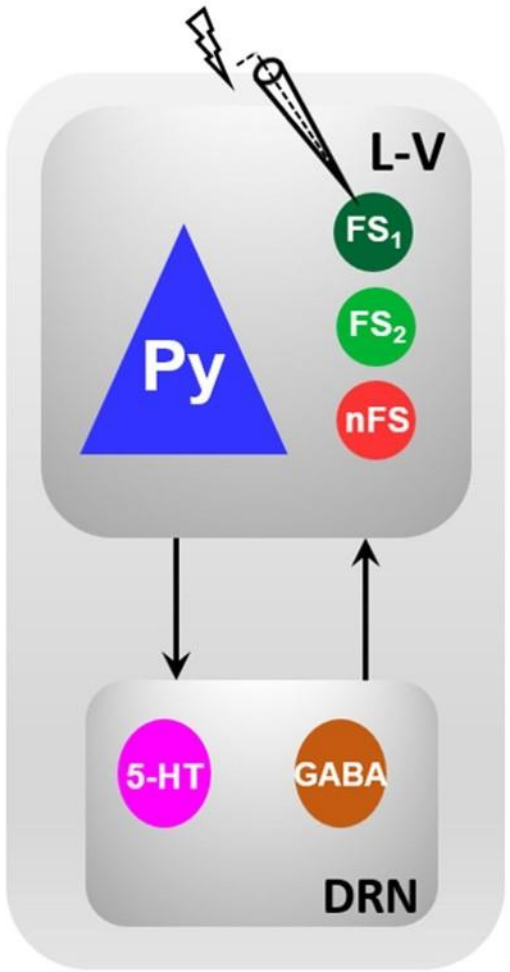


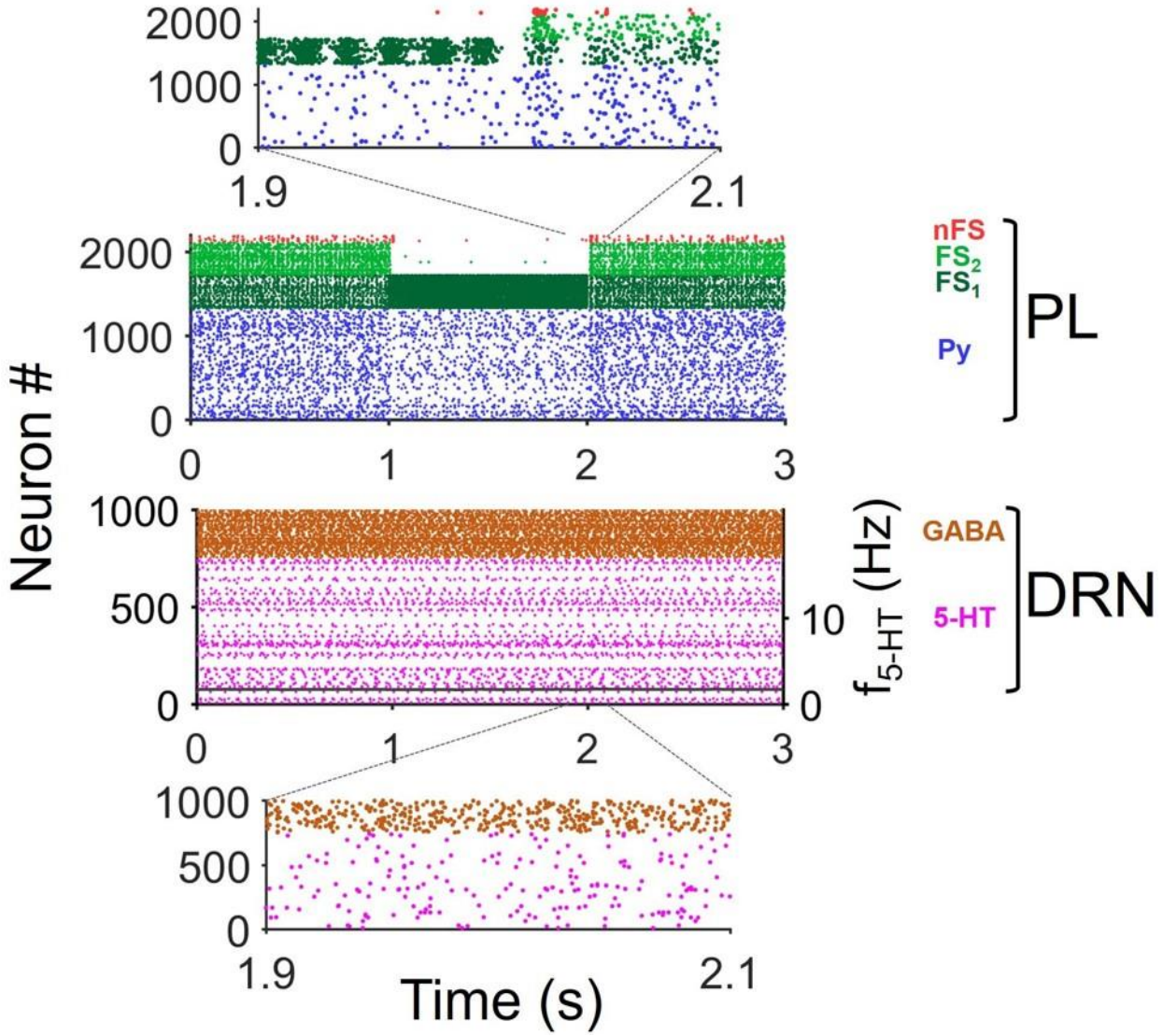
Stimulation of PL pyramidal neurons transiently activates DRN 5-HT and GABAergic neurons





Stimulation of PL interneurons have negligible impact on DRN 5-HT and GABAergic neurons





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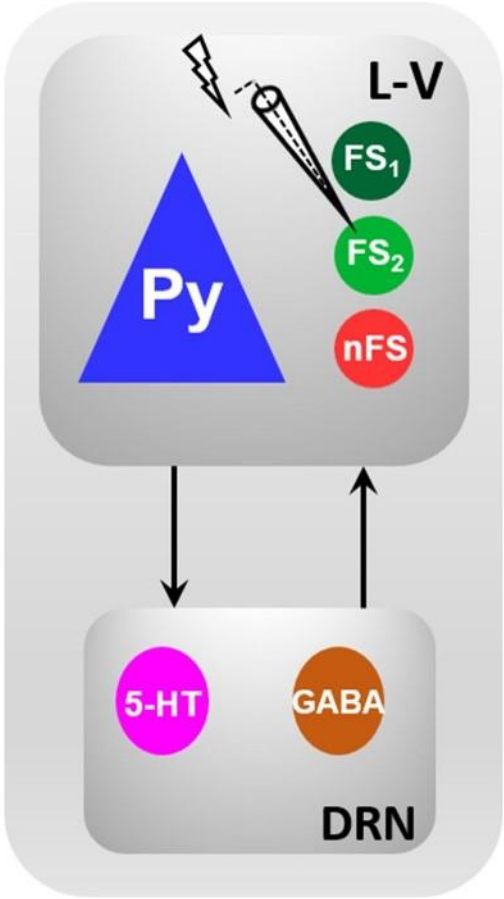

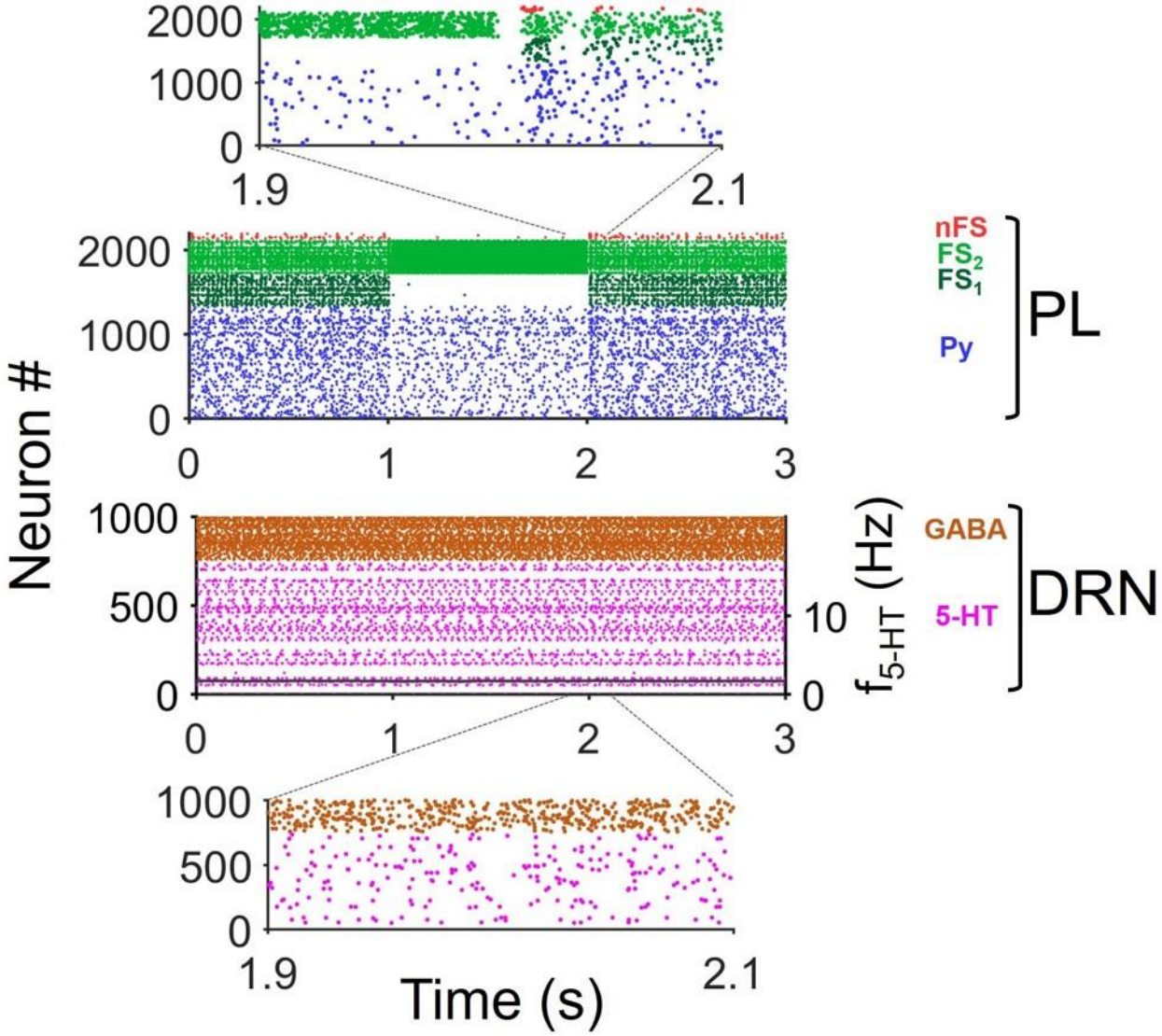

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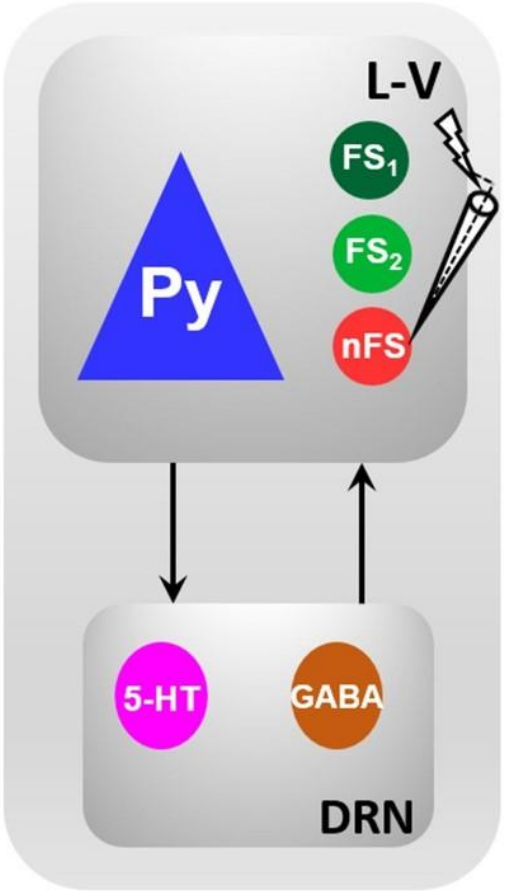
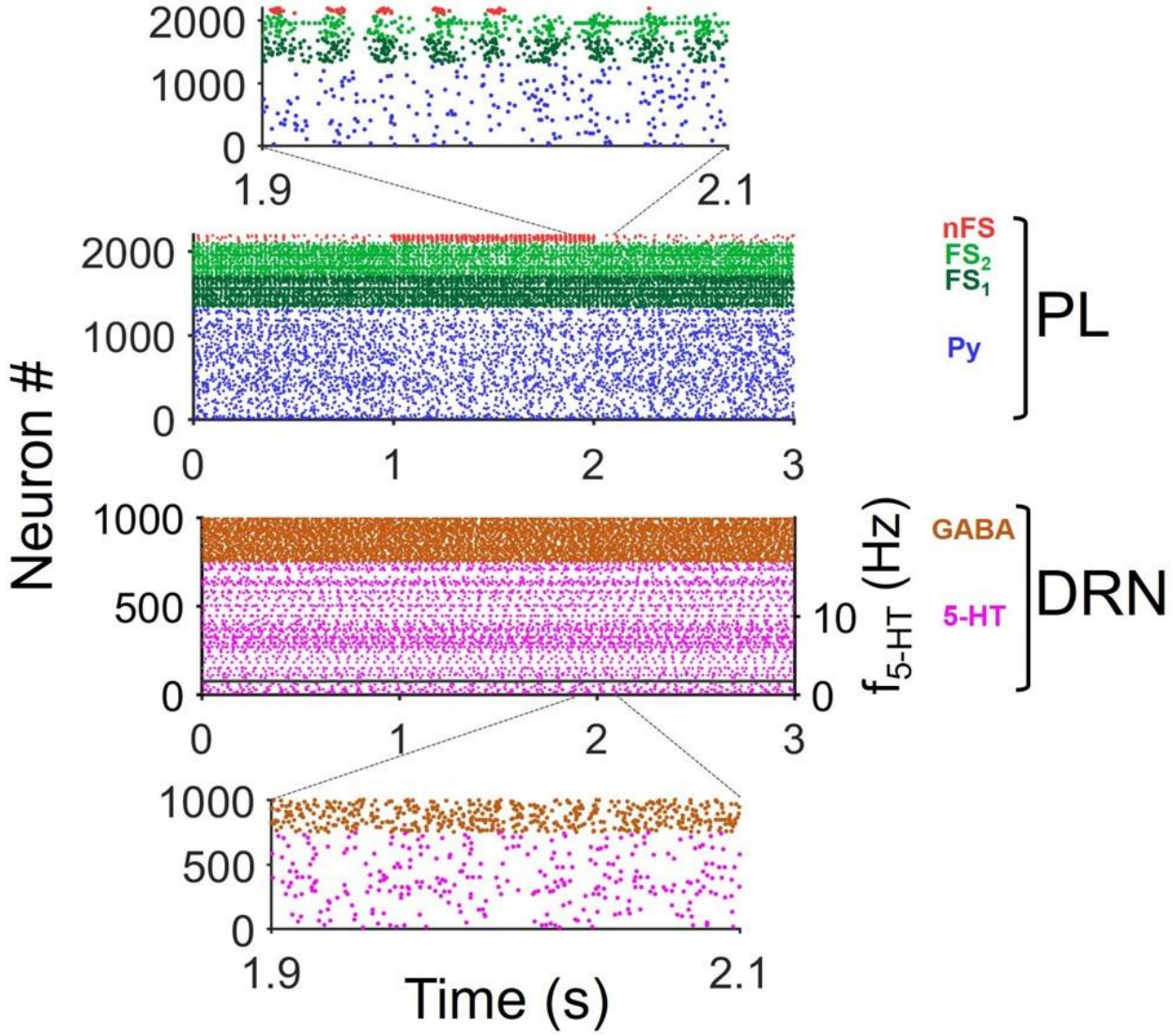
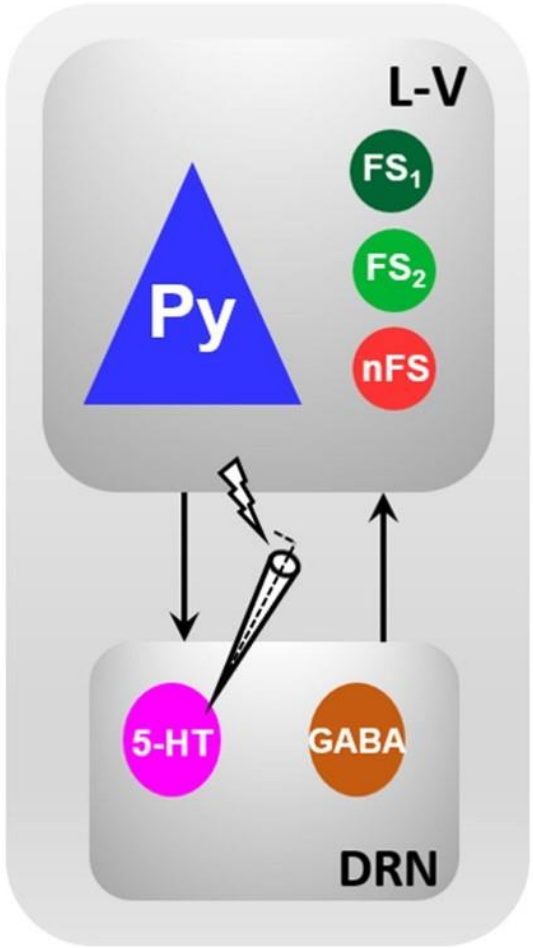
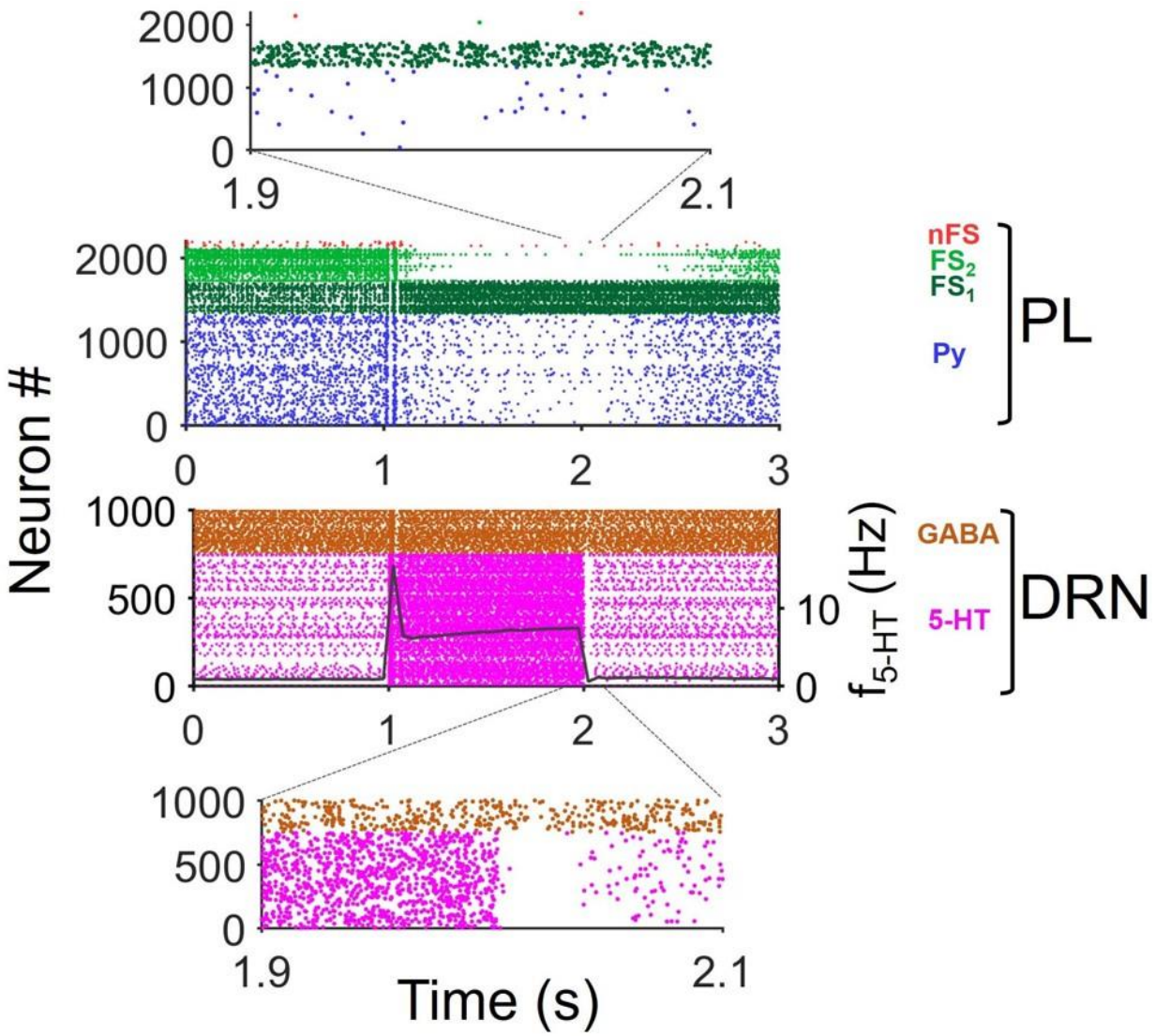


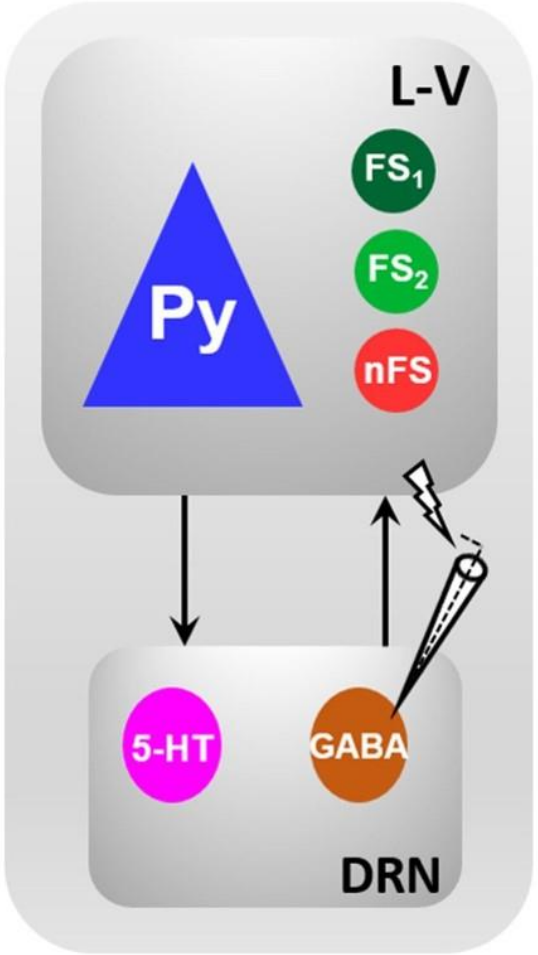


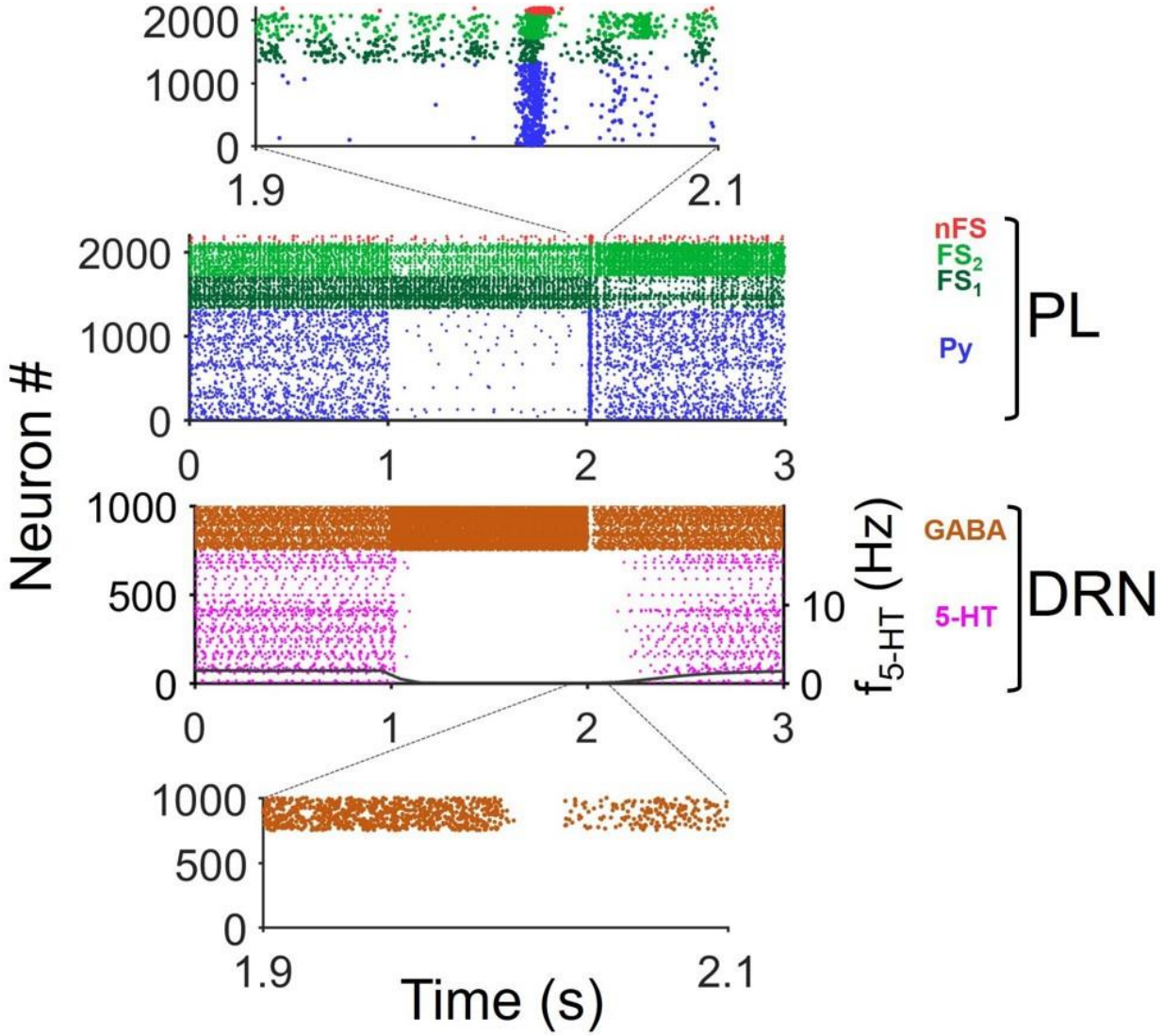
5-HT stimulation activates 5-HT neurons and inhibits Py neurons



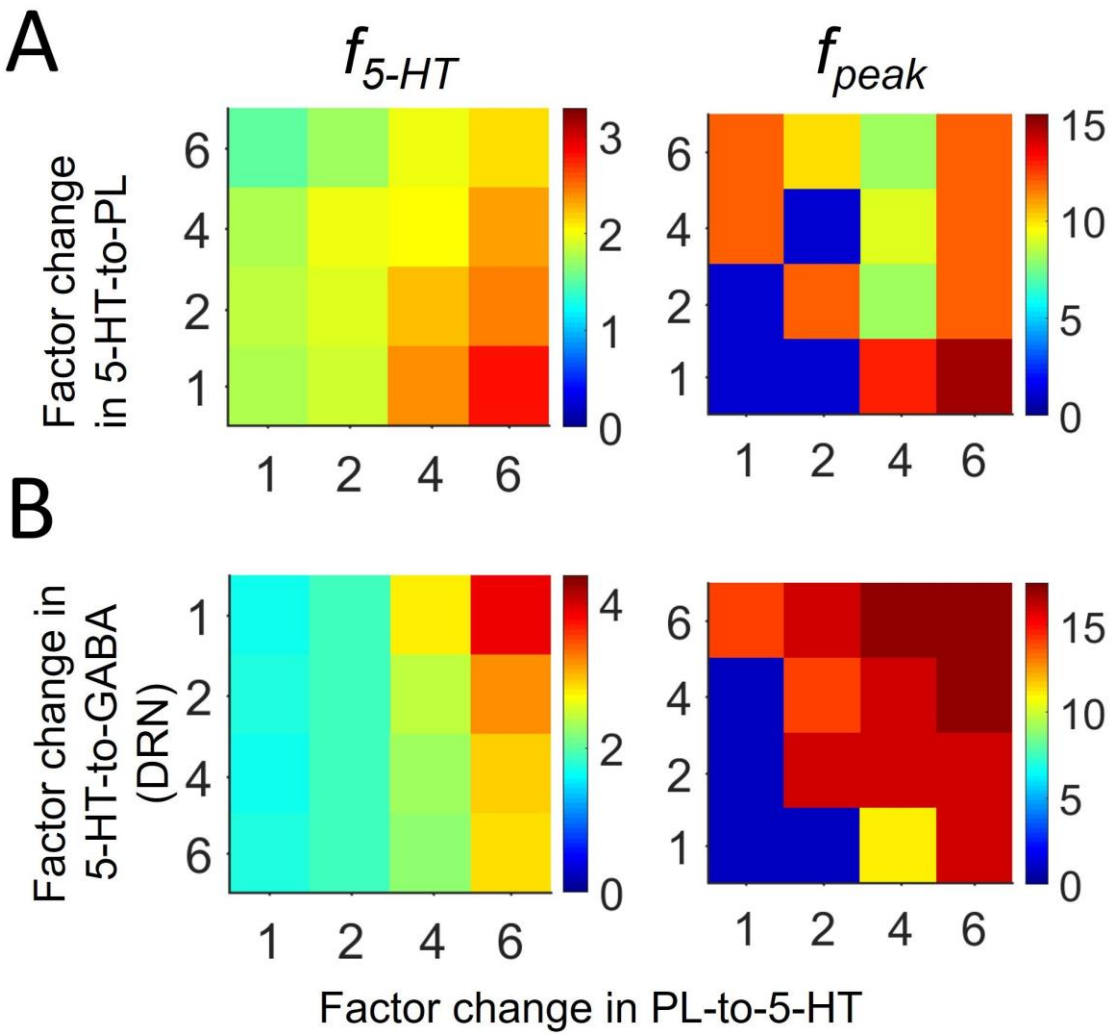


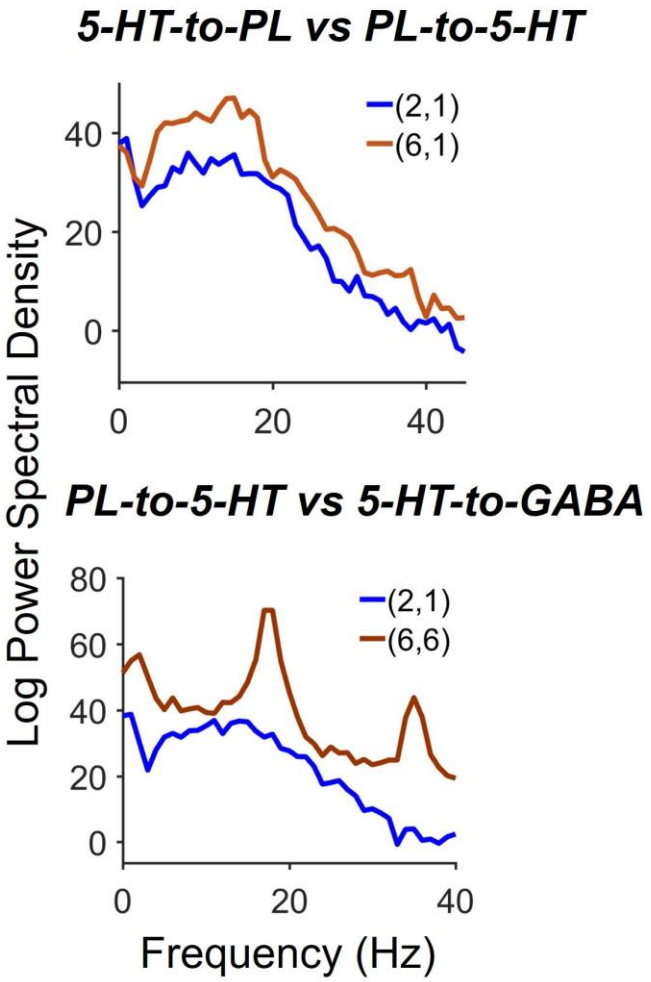
GABAergic stimulation is stronger than 5-HT and inhibits significant Py and 5-HT neurons





Stronger long-range PL-to-5-HT or local short-range 5-HT-to-GABA connections, enhances higher DRN frequency oscillations





Conclusion

- Developed the first closed-loop model of the PFC-DRN, focusing on PL.
- Model supports co-existence of baseline firing activities and multiple network frequency bands observed in various separate experimental studies.
- Stimulation of PL pyramidal, but not PL GABAergic, neurons transiently activates DRN 5-HT and GABAergic neurons.
- Stronger long-range PL-to-5-HT or local short-range 5-HT-to-GABA connections, enhances higher DRN frequency oscillations, primarily mediated by DRN GABAergic neurons.
- Computational model lays the foundation towards developing more realistic closed-loop neuronal circuits for systematic understanding of chemical neuromodulation and its links to cognition and brain disorders.

Acknowledgements

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